review has been noted by subsequent authors (2914). The etiology of lung cancer was discussed by Hueper in both articles (2623, 2933) and are detailed in Topics D and E. The subject of tobacco smoking was discussed as follows:

> "The causes classified in the second group are those of physical means. A trauma of the chest is too rare a cause of a lung carcinoma to have any relation to the increasing frequency of these tumors. Also the suspicion mentioned by Kukuth that the increasing use of X-rays for the treatment and diagnosis of thorax diseases might have some connection with the increase of the lung carcinomas seems to be unjustified because the frequency of the lung carcinomas does not correspond to the increase in the use of X-rays, and even Kikuth could not establish this connection in his material. Furthermore we may eliminate the inhalation of cigarette smoke as a causative factor for this incrase, as stated by Fahr, who based his theory on the increased habit of cigarette smoking and the predominance of the affection in the male sex. Cigarette smoke may have only a contributory influence if any at all. A theory of more importance is supported by Hampeln. He believes that a certain relation exists between the increased production of smoke and dust in the big cities which are substances causing by continuous inhalation a chronic irritation of the bronchial and lung epithelim, and the increasing frequency of the lung carcinomas. This theory, like that concerning the influenza epidemic, seems to be quite acceptable at first view, but the investigations of other authors (Dynkin, Sachs, Berblinger) failed to substantiate this presumption. They were unable to state a higher frequency of carcinoma in pneumonoconiotic lungs than in other lungs. Schmorl denies also a causative connection between the well known lung carcinoma of the Schneeberg miners with a primary pneumonoconiosis. He is rather convinced that these tumors are caused by the chemical effect of inhaled gaseous substances and suspects that arsenic compounds have to be made responsible for the frequent development of carcinomas in the lungs of these miner." (p 85, ref. 2623)

There are more samples of differing opinions on etiology of lung cancer appearing in the remainder of this subsection. However, Hueper was the only one who continued to support, during the next four decades, the theory that industrial or occupational exposure is more important than personal tobacco use in association with lung cancer.

Animal experiments on tobacco tar. At the time that fossil fuel products and combustion emission were demonstrated to cause experimental cancer in the skin and lung (see Topic D), similar tests using tobacco gave negative results. Leitch had successfully induced coal tar skin cancer in mice (2221, 2322, 2417). However, his tests of tobacco tar gave the following results:

> "We set an artificial pipe where the tobacco was smoked by suction from a water pump and collected that fluid products of combustion, such as are found in the stem of an ordinary pipe. These products consisted of a brown tarry material easily soluble in chloroform or ether, and a light-coloured watery fluid which darkened through time or by oxidation. The latter fraction, tested on mice for over a year, was without toxic properties and produced no pathological effects whatever. The chloroform-soluble fraction, with the solvent driven off, had, on the other hand, both toxic and pathogenic properties. A minute trace of it applied to the mucous membrane of the tongue or of the vagina, or even to the skin, of rats and mice brought about death by clonic convulsions, usually within a minute. This poisonous effect is probably due to nicotine. By diluting the tarry faction with acetone to 5 per cent. and afterwards gradually increasing the concentration we found that we could accustom the mice finally to the undiluted stuff. Again, we boiled the tobacco is water first of all in order to deprive it of nicotine and obtained a non-toxic product by smoking. We applied these fractions to two series of mice for many months. They produced epilation of the areas to which they were applied, and they induced chronic ulcerations, but in no single case did any neoplastic reaction result. We have thus no evidence in support of the contention that tobacco smoke contains a cancer-producing property, though we may not therefore conclusively reject the idea that there is something connected with tobacco-smoking which may be operative on the oral mucous membrane of human beings. But what is of more theoretical and practical interest is the fact that here we had a substance with a very marked irritative effect on the skin in that it produced chronic lesions and yet no tumour formation supervened. We might say that it is not a specific irritant of the tumour-producing class." (p 6, ref, 2322)

The above three articles by Leitch were overlooked by Harris although they were mentioned in the 1964 Surgeon General Report and as secondary reference in a representative key article selected by Harris [cited in P129].

Helwig, a pathologist at the University of Kansas, was aware of experimental coal tar cancer but it "seemed incredible that the literature is so barren of any experimental data regarding the use of tobacco or its extracts" (2720). He found only one instance "wherein the use of tobacco tar produced any typical epithelial proliferation. Wachter and Schmincke, in 1911 used the tar obtained from tobacco pipes mixed with oil and produced an atypical proliferation in rabbits ears." Since there were no subsequent studies on tobacco, Helwig proceeded as follows:

> "With these foregoing facts in mind, I began in 1925 on an experiment of this nature. In order to familiarize myself with the technic and early recognition of the changes that might result, it was thought best to duplicate some of the work done with soot. Typical 'chimney sweeps' warts, which progressed to malignancy, were produced in mice by painting the backs of their heads with soot extract, according to the method of Kennaway and Passey. A strain of albino mice of low spontaneous cancer incidence was chosen, and it was possible to produce typical infiltrating squamous cell epithelioma with this product. A small series of fifteen mice were chosen. At the end of three months from the beginning of the experiment, five of the fifteen mice had developed warts and four had died of intercurrent infections without trace of either warts or other evidence of tumor. In the following month eight of these eleven had died, leaving three with warts. One of these subsequently died, not going on to malignancy. The warts of the other two mice grew very rapidly during the ensuing month and at the end of this time both were very large, ulcerating, fungating masses. A biopsy from one showed a typical squamous cell epithelioma. After the biopsy this animal died and there were no metastases. The other animal lived for a month longer and died with an enormous ulcerating cauliflower mass covering the entire top of his head and shoulders, which tumor was typically malignant.
>
> I then duplicated the work of Wacker and Schmincke, taking the tobacco tar from the bowls of briar pipes and mixing the etheral extract with olive oil. This product was injected in the skin of rabbits' ears and atypical proliferation took place, but never an actual malignant transformation. On one of the rabbits, a biopsy was done after four months, and even here a large keratinized mass surrounded by epithelium was seen. Also, the proliferation in one rabbit was so marked as to break through the cartilage, but it was not progressive; nor were subsequent injections ever capable of producing a limitless growth.

Mice were chosen because of the well known fact that they are particularly susceptible to irritation tar neoplasms, in contra-distinction to rats. Tar is used on rats with no success, but in mice some men have been able to produce an incidence of tumors approaching 100 per cent. Systematic painting of the backs of the heads of mice was begun with an ethereal extract of tobacco tar. This tar was extracted from briar pipes. A large series of mice were painted and it was found that the product was highly toxic. The nicotine was therefore extracted by shaking with diluted hydro-chloric acid. This product was found to be nontoxic. Fifty mice were painted three times a week over a period of almost one year. It was thought best to epilate the hair with barium sulphide and the painting was started. Ulceration of a rather marked degree was produced and at intervals sections were taken from these ulcers, but no atypical growth was ever encountered. In some cases in which the ulceration was too severe, the painting was reduced to once a week until the ulceration partially healed.

At this time I communicated with Dr. Archibald Leitch, director of the Cancer Hospital Research Institute in London. He had been having striking results with various tars and oils. To my surprise, I learned that he had been trying a similar experiment to mine, producing his tar by artificial 'smoking.' This he accomplished by putting tobacco in a Buchner filter funner attached to flasks acting as condensers, which were in turn attached to a filter pump. He produced a chloroform-soluble tar which caused ulceration but no epithelial proliferation. He felt, however, that an effective product could be obtained with a higher temperature of combustion. The idea was already in my mind, as I knew of his experiments with high temperature coal tar distillates.

I made a large iron combustion still and heated tobacco to a temperature of between 400 and 500 C. The resulting tarry product was extract with ether and chloroform and the two extracts were applied to a series of fifty mice. As in the former case, nothing but ulceration resulted. This product was not toxic after the nicotine had been extracted but was very irritating. The ulceration was very extensive in some cases, and painting had to be suspended from time to time. This was carried on for about eight months. Most of the mice lost weight and died of pneumonia. In none of this series was any atypical epithelial growth encountered. When the painting was suspended, the ulcers healed promptly. No warts were produced." (p 151, ref. 2827)

The addition of olive oil or glycerin was for the purpose of preparing a suitable vehicle for dermal application as well as to reduce early death from absorption of tar constituents. A similar solvent was used in coal tar testing described under Topic D below. Helwig's negative studies on tobacco tar was

overlooked by Harris in his SOA report. However, four articles used by Harris as representative key articles alluded to Helwig's article as a secondary reference: P81 Flory, P24 Schreck, P264 Suguira and P291 Wynder. There was ample opportunity for Harris to notice Helwig's study.

Animal experiments on tobacco smoke exposure. Although tobacco smoke had already been analyzed for contents of nicotine (2323, 2723), the technique was not applied to the study of nicotine absorption. The effect of nicotine on ciliary movement was examined in excised trachea in organ bath (2830). An in vivo lung preparation was not yet available for testing of lung function. There was an animal guinea pig model for study of tumor-like formation caused by silica dust (2831). Histopathologic studies pf experimental fibrosis in guinea pig (2225) and jagziekte or adenomatosis in sheep (2521) demons- trated that alveolar phagocytes could contribute to pulmonary carcinogenesis. There were animal studies indicating that diet influenced the growth of non-pulmonary forms of cancer (2625, 2832). There were early results on influence of hydrogen and salts on growth of transplanted rat carcinoma (2123, 2125) but it would take two decades before this technique would apply to pulmonary carcinogenesis.

D. Fossil Fuel Products and Combustion Emission

During the bicentennial commemoration of Percival Pott's description of scrotal cancer, Kipling and Waldron reviewed the events leading to the identification of the cause (7511). Even after the passage of Chimney Seepers Act in 1875 to protect employment of children in England, the debate continued as to the identity of the causative agent. Pott himself did not speculate on the cause and it was generally assumed that the lodgement of soot in the rugae of the scrotum was the cause. In 1878, Lawson made the suggestion that the cancer was really caused by friction between the sweeper's overalls and his scrotum as he was sifting the soot to remove debris prior to its sale. Fifty years later this frictional theory was applied to mule-spinners cancer, instead of mineral oil which the majority held to be the causative agent (2727, 2824). The soot debate was finally resolved by Passey who showed in 1922 that skin cancer in mice could be induced by an ethereal extract of soot (2220). The carcinogenic action of fossil fuel products and combustion emission was supported by human studies and animal experiments. The proof was essentially complete for skin tar cancer. The causation of lung cancer by fossil fuel products and combustion emission was gaining widespread acceptance because the increasing incidence in humans coincided with widespread use. Animal experiments supported the concept that intratracheal administration of coal tar caused lung cancer.

Occupational tar cancer. In 1925, Alice Hamilton, Professor of Industrial Medicine at Harvard Medical School wrote her monograph entitled Industrial Poisons in the United States (2501). At that time, she regarded the literature concerning skin lesions in workers with coal tar and petroleum

oils, paraffin, vaseline, soot, pitch, shale and related products, was confusing. The reason was as follows: "It is impossible in most instances to gain any clear idea as to just what substances are playing a part in the acne, furunculosis, warty growths, keratomalosis, plaques or cancers, which are described, and often it is hard to make out whether the skin lesions are due to chemical irritants or caused simply by mechanical agents such as the plugging of sebaceous ducts or injury by sharp bits of metals with subsequent infection." In 1926, W.H. Woglom of the Institute of Cancer Research, Columbia University, published his comprehensive review entitled Experimental Tar Cancer (2601). The section on industrial tar cancer reflected the varied forms of exposure:

> "It has been known for years that those whose occupations expose them to soot, tar, or similar substances are prone to develop cancer, and the conditions governing its occurrence have been to some extent delimited.
>
> Thus Ross has observed that blast furnace tar, though similar to coal tar, except that it is distilled at a lower temperature and from a different variety of coal, appears to be harmless, whereas gasworks tar causes warts and epitheliomas on the hands and arms of the workmen who handle it; the incidence is not so high, however, as in the case of pitch or soot.
>
> Differences in the nature of the coal employed have been advanced by Courmont to explain the frequency of industrial tar cancer in England and its extreme rarity in France.
>
> A prolonged exposure to the irritant is usually necessary, ten years having been the shortest period in the experience of O'Donovan, and forty years the longest. In one case the patient had not handled tar for twenty-eight years, and this writer cites an instance recorded by Bland Sutton in which soot cancer developed thirty-five years after the cessation of exposure.
>
> Age did not seem to be a factor of importance in O'Donovan's series. In sixteen patients, the carcinoma developed at: 33 to 39 years in 4 cases, 40 to 49 years in 1 case, 50 to 59 years in 3 cases, 60 to 69 years in 6 cases and 70 to 75 years in 2 cases.
>
> O'Donovan regards the prognosis as good, and says that papillary tumors that have microscopically been proved carcinomatous have generally fallen away after from two to four months' duration.
>
> In this his experience has been similar to that of others. Schamberg, for example, regards as a notable feature of tar cancers

their frequent tendency to undergo spontaneous involution, and says that older writers have remarked on the benign nature of chimney sweeps' cancer of the scrotum.

The almost universal restriction of this epithelioma to the scrotum has been the subject of considerable discussion since the disease first came under observation, but Kennaway has recently called attention to the fact that other occupational cancers also have a definite site of election. Two thirds of all pitch cancers occur about the face or scrotum, other parts, equally exposed to pitch dust, seldom being affected. In mule-spinners' cancer the scrotum is again the site of election, although the penis and a wide area of skin on the abdomen and thighs are equally exposed to the oil which causes this neoplasm. In aniline dye workers, cancer develops almost always in the bladder, and on its posterior wall; while in persons taking arsenic, it is the fingers, legs and trunk that are most often attacked. In coal miners and agricultural laborers, carcinoma involves the penis much more frequently than the scrotum; therefore, says Kennaway, neither the rugosity of the scrotum nor the abundance of its sebaceous glands can explain the frequency of cancer at this site in certain trades.

The carcinogenic activity of mineral oils, which cannot be gone into here, has been discussed by Scott and Leitch.

Although years of exposure are usually necessary for the development of occupational cancer, as has already been indicated, this seems not invariably to be true. Thus Huguenin has described the case of a workman, aged 35, who had often suffered burns from droplets of crude oil, which had left no trace. In the present instance, however, the hot oil fell on the recent scar of a deep burn received from a charcoal stove, where it caused a burn of the first degree. One week later a small papule appeared, which grew so rapidly that it had attained the size of a walnut within twenty-five days. Histologic examination of the extirpated nodule showed that it was a keratinizing carcinoma.

Bang has reported a somewhat similar instance in a gas retort workman, in whom cancer of the nostril developed sixteen days after a tar burn.

The preceding cases have been cited, not with the idea of giving even a fragmentary review of industrial cancer, but because there is not one but what can be matched in the laboratory. The similarity between industrial tar cancer in man and the experimental tar cancer of certain laboratory animals is close indeed." (p 534, 535, ref. 2601)

Four years after the appearance of the above review articles, Woglom and Herley reported results of skin painting in mice (2934). The tar used was a horizontal retort gas-works product distilled at about 1000 C. Even with the

dilution to 25 percent tar in glycerin, malignant tumors were produced with lower mortality compared to undiluted tar. The varied sources of coal tar continued to be tested during the 1930's to seek confirmation on causation of tar cancer seen in human skin.

Cancer producing tars. Kennaway (2415) reviewed the seven forms of tar reported to produce skin cancer in workers: (a) wood tar; (b) lignite tar; (c) water-gas tar; (d) gas-works tar from horizontal retorts and vertical retorts; (e) blast-furnace tar; (f) coke oven tar; and (g) producer-gas tar. The last four, (d) to (g), were derived from coal and referred to as "coal tar."

> "It is known that of these, lignite tar, gas-works tar, producer-gas tar, and probably coke-oven tar, produce cancer, while blast-furnace tar does not. We seem to have no information regarding wood tar and water-gas tar in this respect; hence these tars need not be further described. What then is the factor which decides whether a tar shall or shall not have cancer-producing properties? In order to consider this question one must first state very briefly the mode of information and the chemical characters of the different tars. The chemical composition of a tar depends largely upon the temperature to which it has been exposed; hence all the avilable data as to the temperatures reached in the various commerical methods of carbonization are of interest in this matter." (p 233, ref. 2415)

Kennaway proceeded to review the industrial evidence provided by official returns from governmental agencies and clinical records of cancer occurring in workmen exposed to various materials. He also listed the known constituents of various forms of tar and reviewed the experimental evidence obtained by application of the materials to mice. However, he could not ascertain the identity of cancer producing constituents occurring in most or all tar products.

Experimental skin cancer. Harris used two publications in the 1920's to justify his statement that "experimental scientists had found that carcinogenic tars could be formed from the pyrogenous products of a variety of organic materials" [SOA 4.5]. One article was by Kennaway and Sampson on the pyrogenous products of cholesterol (2825), and the other by Kennaway on yeast, human skin, Durnham coal, California petroleum, isoprene, and acetylene (2517). The last mentioned hydrocarbon, heated from 700 to 900 C, was the simplest organic compound from which a carcinogenic material has so far been obtained during the 1920's. Three other articles by Kennaway were not mentioned by Harris: the first one on isoprene (2416), the second one was a review article stated above(2415), and the third one was on anatomical distribution of occupational cancer (2524). Harris also omitted the following German publications on experimental skin tar cancer: Hueper (2311), Roesch (2326), Steinbrück (2949), Schabad (2948), and Oppenheim (2420). Twort and Fulton (2917) from the University of Manchester reported the results of skin painting studies in mice. They concluded that in fractional distillation of carcinogenic oils (American petroleum oils, shale oil), the active agent was concentrated in the higher, and sometimes in the lower, fraction. Carcinogenic activity of an oil was much reduced or completely removed by extraction with sulfuric acid, by oxidation and by reduction. Final identification of active constituents would await studies conducted during the 1930's.

As stated above, Passey (2220) was accredited by medical historians to have obtained first unequivocal evidence that scrotal soot cancer is due to chemical irritation instead of mechanical irritation. His publication was

entitled Experimental Soot Cancer and appeared in abbreviated form (2220) as well as in detailed form (2518, 2519). Harris cited the former [SOA 184] but not the latter in support of the following: "Similarly, Passey's 1922 experimental finding of the carcinogenicity of soot extracts confirmed the frequent clinical observation of cancer in soot-exposed workers" [SOA 4.4]. There are details that may prove pertinent to a future questioning of Harris.

Experimental lung cancer. This subject was not discussed by Harris even though there was positive information that coal tar caused lung cancer in experimental animals. Murphy and Sturm reported lung tumors in mice following cutaneous application of coal tar (2520). Kimura used "intrabronchial insufflation", i.e., "forcing a small amount of crude coal-tar into the bronchus through the tracheotomy wound of animals previously anesthetized completely." He reported "a small adenomatous area in the rabbit lung and a multiple adenocarcinoma in one of the three guinea pigs" (2321). Smith (2826) exposed mice to coal pitch distilled at 346 C which corresponded as nearly as possible to that used by Murphy and Sturm. The coal pitch was heated on an iron tray over a Bunsen burner inside a chamber. The exposure lasted for six hours a day, five days a week during the first three months, and after that, for three times a week. None of the 20 animals developed a tumor of the lung after exposure ranging from 36 to 141 days. This negative study is less convincing than the positive studies.

Environmental dust and smoke. Hueper summarized the German literature relating to causative factors of chemical nature (2623, 2933):

> "We can eliminate from the list of the possible or suspected chemical factors which may be responsible for the increasing frequency, all those which have no generalized distribution and to which we are exposed to a certain degree for a period longer than

> the last twenty years. This consideration excludes the theory of Kraus proposing a relation of the gas poisonings during the war with lung carcinomas. By far the majority of the cases were never exposed to this injury. Furthermore, we can neglect the inhalation of acids and alkalis as unimportant in this question. A theory which fulfills the above mentioned conditions was expressed by Stahelin. According to him the main factor responsible for the increase of the lung carcinomas in the last fifteen to twenty years is not the inhalation of smoke dust but the inhalation of dust containing chemical substances which possess a specific carcinoma-producing quality. He believes that the small tar and oil particles in the dust of tarred or oiled roads and the oxidation products of gasoline and benzol, daily inhaled in large amounts, are the causative factors for the increase.
>
> His theory is based on the following viewpoints: (1) the tarring of the roads and the more general use of gasoline for automobiles date back about twenty years and have increased rapidly since that time; (2) tar products are recognized as carcinoma-producing substances in case of chronic application; and (3) carcinoma of the lung in rabbits and guinea-pigs was produced successfully by injection of tar products in the trachea (Kimura). This theory is based on several very important facts and is worth examining on a broad experimental and statistical basis. Its practical importance is obvious in a country which has the most tarred roads and automobiles in the world." (p 86, ref. 2623)

The theory proposed by Staehelm that tarring roads and streets is the cause of increased incidence of lung cancer has been cited in an editorial of the Journal of the American Medical Association (2624). Since the increase of lung carcinoma incidence during the previous decade was proportionately less than in carcinoma of other parts of the body, the applicability of the theory based on German statistics was questioned for the United States (2619).

In a later review by Hueper, he discussed the role of pollutants in the ambient air:

> "Dust and smoke, especially coal and quartz dust, which produce an anthrakosis and chalikosis of the lung with resulting chronic interstitial pneumonia and a chronic bronchitis with secondary regenerative metaplastic changes and proliferations of the bronchial mucosa and alveolar epithelium are considered by many as etiologically important factors and are regarded by them as those causative

> agents which are responsible for the recent marked increase in frequency of these tumors because the production of smoke and dust has grown considerably in the big cities during the last two decades (Rostoski, Saupe and Schmorl, Hampeln, Schmidt, Ewing, Brandt, Ferenszy and Matolszy, etc.). The higher frequency of lung carcinomas in horses and dogs which are exposed to the inhalation of dust and smoke against that of cattle seems to support this conception. Probst, however, as well as Berblinger, Dynkin, Sachs and others could not state a higher frequency of lung carcinoma in persons which are especially exposed to the inhalation of these substances.
>
> Tobacco smoke is also mentioned among the agents responsible for the production and the increased frequency of these tumors (Seyfarth, Fahr, Heilmann). The frequent occurrence of lung carcinomas among waiters, cigarette workers and members of similar professions and the predominance of these tumors in men who more often indulge in excessive smoking of cigarettes are emphasized by these authors in support of their contention." (p 297, ref. 2933)

The above quotations from Hueper's publications during the 1920's should be recalled presently because earlier German publications are cited. Most arguments if favor of fossil fuel products and combustion emission were continually repeated during the next four decades.

Simpson, a pathologist at the London Hospital, commented that clinically there was as yet no direct correlation of tar with carcinoma of the lung:

> ".... It is true that there has been an enormous increase in the practice of tarring of the roads, but there is not sufficient evidence to justify correlating the fact with the increased incidence of carcinoma of the lung. The fact that carcinoma of the lung is very rare in places like Hong Kong and Singapore, where the roads are not tarred, is possibly suggestive. The obtaining of statistics to investigate any co-relationship between the extent of tarring of the roads and the incidence of carcinoma of the lung in different districts and different countries offer many difficulties; but when one considers the widespread practice of tarring (half a million tons of tar are used annually in this country), the known potentialities of tar as an irritant factor, and the undue proportion of males and outdoor workers, it is obvious that here lies an urgent problem that demands scientific solution.
>
> As regards the less specific irritants met with in the streets, and the various combustion products of motor engines, there is no available scientific evidence." (p 438, 439, ref. 2927)

I have not found the lung cancer statistics for Hong Kong and Singapore. However, the report of Sison and Monserrat on rarity of lung cancer in the Philippines may be substituted: "since the establishment of the City Morgue in Manila and up to October 1925 (about 18 years), only one case of primary carcinoma was observed among 11,599 autopsies performed ... the 2 cases that came to our observation were admitted in the Philippine General Hospital within a period of a little more than two months, and yet during the 18 years only one case was autopsied in the City Morgue, ... and for 15 years since the Philippine General Hospital was established, not a single case of primary malignant growth was reported except our two" (2718). The rarity of lung cancer may conform to the theory of Staheilin because road asphalting was rare in the Philippines during the 1920's.

Occupational history of a significant number of lung cancer case reports support the theory that fossil fuel products and combustion emission are etiologic factors. Duguid (2721) examined the occupational history of 143 males with lung cancer:

> "The largest number in any single occupation was found amongst labourers and of these there were 28. Next to them in order of numbers came carters, of whom there were 9, and next to these clerks, numbering 8. In none of the other occupations were more than four cases recorded. It was found on counting the labourers in the former class that the outdoor and indoor workers were nearly equal proportion, there being 72 outdoor to 71 indoor workers. The number of men who had described themselves as carters was striking, and this drew attention to those who registered occupations closely related in one way or another to that of carter. These total 25, and are set forth in the following list: Carters, 9; van drivers, 2; lorrymen 1; coachman, 1; teamster, 1; horse keepers, 2; ostler, 1; stablemen, 1; tram drivers, 3; engine drivers, 2; tram guard, 1; railway guard, 1.
>
> These represented all the transport workers in the list, so that such workers constituted 16.55 per cent. of all male cases.
>
> With the help of a census list kindly supplied by Dr. W.S. McClure, of the Department of Public Health, Manchester, it was

> possible to compare the percentage of tumour cases in the various occupations with the percentage of the whole male population of Manchester in these occupations. It was found impossible to estimate with accuracy the numbers of outdoor and indoor workers, because many of the occupations specified in the list included workers in both these classes, but it could be judged that at least 75 per cent. of the adult population were indoor workers. Since, therefore, in the cases of tumour there were actually more outdoor workers than indoor ones, it may be concluded that the incidence is higher in the former class in a proportion of three to one. In the census list it was found that the transport workers constituted 12.34 per cent. of the total male population, whereas in the case list these workers, as stated above, constituted 16.55 per cent. of the male cases. In none of the other occupations were the numbers of cases large enough to allow of useful comparisons being made." (p 112, ref. 2721)

The above publication by Duguid (2721) was the subject of Tylecote's letter to Lancet (2719). Harris used the latter (SOA 189, DTH 85, P271) without mention of Duguid's publication that support occupational cause of lung cancer.

E. Hostal Susceptibility Factors

The 1920's was the period when eugenicists were most active in soliciting the cooperation of geneticists. Clarence Cook Little was then the President of the University of Michigan, and moved to Maine to organize the Jackson Memorial Laboratories. Harris cited one page of a book by D. J. Kevles entitled In the Name of Eugenics, when he was questioned if he knew of Little [ERR 24]. In Kevles' book (8501), Little is characterized as a leader of "eugenic priesthood" and used other phrases for Eysenck and Fisher who will later play important roles in the constitutional hypothesis of lung cancer (see Part V). That Harris is familiar with Kevles' book is relevant as to whether Harris was aware of racial prejudices that influenced scientific opinion during the 1920s. To pure eugenicists, racial superiority meant resistance to diseases, and racial inferiority meant susceptibility to diseases. Geneticists did not believe that environmental factors would cause cancer. Statisticians, who were also mathematicians, included eugenicists and geneticists. Each scientist had his own racial and social background that would influence their concepts on hostal susceptibility to environmental factors causing lung cancer.

Heredity. Clarence Cook Little was not the only geneticist interested in comparing lung cancer incidence of Jews and Gentiles [see ERR 24]. Several clinicians routinely questioned patients for racial background as to whether they were Jewish, Russian, Polish, Mexican, or otherwise (2827, 2312, 1811, 2812, 2215, 2513). A case report of lung cancer patient with mental illness (2011) raised the question of eugenics of mental disease which was debated during the 1920s. Elida Evans, a student of Dr. C. G. Jung (Founder of Zurich

School of Analytical and Synthetic Psychology), wrote a book entitled A Psychological Study of Cancer (2602). Evans noted the similarities in histories of cancer patients, forming a separate set of "phychological eccentricity." She analyzed over a dozen case histories, all of them with cancer not involving the lung. In an addendum to her book, Evans quoted a press release from the London Bureau of the New York Herald Tribune, July 1, 1926:

> "A pessimistic view is taken of the campaign against cancer among the research workers of this country as the British experts prepare to attend the world conference called by the American Society for the Control of Cancer at Lake Mohonk in September. The feeling in this country is that the cancer experts of the world are more successful exploding one another's theories than they are in finding the causes of, to say nothing of the cure for, cancer.
>
> 'We are no further forward,' was the frank admission made today by Sir John Bland Sutton, distinguished surgeon and one of the leading cancer authorities in Great Britain. A year ago, Gye and Barnard thrilled the world with the report that they had discovered the germ that produced cancer and tumor, but, as time has gone by and nobody has succeeded in confirming Gye's brillant theory, a feeling of discouragement has again surged over the promotors of the cancer research campaign in England.
>
> 'Three years ago the British Empire cancer campaign committee launched a appeal to the British public for $5,000,000. According to a member of this committee, only about $600,000 has actually been raised. He stated that about $750,000 had been spent in Great Britain since 1923 fighting cancer, but he had to confess that the results so far have been of a negative character.
>
> 'This is confirmed by Sir John Bland Sutton, who, on being asked if there is any prospect of an early solution of the cancer problem, replied: No. There is an enormous amount of research going on, but, frankly, we are just where we were.'
>
> Those who have read the preceding pages will see that these reports bear out my contention that the growth of the embryo and the malignant growth are in the beginning the same, both being an impulse of growth. One growth comes from an orderly, conscious, creative impulse of union, the other comes from an impulse to increase in the unconscious without union. Each is a reaction from the same elemental law of growth, one an increase from natural law, the other an increase from a thwarted law of nature, whose working is far less easily discernible in animals of lower scale. It is

> highly regrettable that such research as is undertaken by the cancer research organizations is confined to animals. The higher the form of life, the greater seems to necessity of protecting the accomplishment of its broadened reproductive aim." (p 224-226, ref. 2602)

The above quotation is understandable after Evans' short book is read. During the 1920's, there was considerable interest in finding the cause of cancer and Evans was one of the proponents of what will be later known as the "constitutional hypothesis." The psychological components responsible for susceptibility to cancer were regarded as hereditary.

Clara J. Lynch of the Rockefeller Institute for Medical Research, conducted animal experiments from the standpoint of heredity as susceptibility to development of tumors of each tissue or of each organ, as if separately. After presenting laboratory evidence that mammary gland tumors in mice was a dominant inherited character, she proceeded to test heredity of susceptibility to lung tumors in mice (2626, 2729). Her conclusions were as follows:

> "1. The occurrence of tumors in the lung in mice is dependent to a certain extent upon the age of the individual. No tumors were found in the lungs of mice less than 8 months old. They occurred with greatest frequency in mice of about 24 months or older. Mice may live to be more than 3 years old without developing growths in the lung. These facts show that the development of tumors of the lung, if hereditary, is a variable character. An individual, genetically a tumor mouse, may live to a great age without showing a tumor if the requisite environmental stimulus (external or internal) is lacking. Sex if effective at all has a comparatively slight influence upon the incidence of lung tumors.
>
> 2. Two strains of mice were studied which exhibit differences in their rates of incidence of lung tumors that are large enough to be significant. The conflict in the evidence from different laboratories as to whether or not tumors of the lung are the commonest type found in mice, is probably to be explained on the basis of a differing hereditary tendency to such growths in differing stocks.
>
> 3. Data from a number of sources indicate that offspring from parents free from lung tumors have a lower rate of lung tumor incidence than offspring from parents one of which had a tumor. If both parents had lung tumors the rate of tumor incidence among their offspring is increased still further.

4. In crosses between mice from strains which have high and low rates of incidence of lung tumor, tumors appeared in about half of the individuals of the first generation and in about one-quarter of the second generation. If the character responsible for the development of the growths is recessive it should not be found in the first filial generation unless both parents are carrying it. There is no proof that the female parents did not carry it but since they were taken from a strain in which the incidence of the growths was but 6.7 per cent the chances seem good that they were free from it. This suggests that the character determining the incidence of pulmonary tumors may be a dominant one.

A dominant character is not expected to appear among the offspring from parents neither of which has shown the character. The numerous instances which have been tabulated in this paper of mice with lung tumors among the offspring of parents free from lung tumors, must be explained on the assumption that tumor susceptibility is not only dominant but variable and that some of the parents which did not actually develop tumors were genetically tumor mice and had the capacity for developing tumors although it was not brought out. As we have already concluded on the basis of the relationship between age and tumor incidence that susceptitbility to the development of lung tumors is a variable character our explanation of the occurrence of tumor mice derived from tumor-free parents is justifiable.

The existence of strains of mice with rates of incidence of lung tumors that differ as widely as do the two that we have studied, the relatively high incidence of pulmonary growths among mice of tumor parentage as compared with mice from non-tumor parents, and the fact that females from a strain in which pulmonary tumors are rare when crossed with individuals from a strain in which they are frequent give a fairly high rate of incidence of the growths among the first and second filial generations, - all these facts indicate that suceptibility to the development of tumors in the lung is an inherited character." (p 353-355,ref. 2626)

During the next three decades, additional studies were conducted on mice strains susceptible to lung cancer. The phenomenon that strains susceptible to breast or lung cancer may be more than a laboratory curiosity. During the late 1980's, the genetic feature for lung and breast cancer is reported to be contained in a single chromosome (see page 23).

Diet and Nutrition. Frederick T. Marwood wrote a monograph on the subject of salt and food preservatives and the cause of cancer (2701). The

dietary theory was the basis for questionnaries on food intake of cancer patients conducted by Hoffman in San Francisco and Philadelphia (3701), and by Lombard and Doering in Massachusetts (2730, 2833, 2839, 2951). Thirty years later, the use of nitrites to preserve meat was criticized because of formation of nitrosamines that are suspected carcinogens (see Part V).

Hoffman discussed the important dietary theories proposed during the 1920's for causation of all forms of cancer. On the occasion of his address on Cancer and Overnutrition, he presented data from his San Francisco cancer survey, with particular reference to gastrointestinal cancer. His conclusions cautioned his audience about interpolating to other forms on cancer.

> "First. Cancer is unquestionably on the increase in all civilized countries, but tending towards a maximum death rate, which is likely to become stationary, unless far-reaching reforms are introduced into the mode of living of modern people, which is largely at variance with the natural requirements of the human body.
>
> Second. The incidence of cancer by organs and parts varies so widely for different localities which may have approximately the same general rate of frequency that it is of the first importance that cancer studies should specialize in particular organs and parts rather than in the general frequency of the disease without differentiation. Causative factors or conditioning circumstances must unquestionably exist which will locally account for these variations and which if ascertained will aid measurably in the gradual solution of the cancer problem.
>
> Third. Cancer is unquestionably very rare in native races not in contact with the customs and habits of civilized populations. The reference here is to carcinomas and not to sarcomas, which are more frequently met with in primitive types of people. The reasons for the profound difference in the cancer liability of primitive and civilized races are in my judgment largely dietary and the resulting effects on the human constitution. Native races live under more natural conditions, eat more natural food, are more free from the nervous tension of modern civilized life and therefore largely exempt from the irritating effects of the multitude of conditions which constitute the background of the cancer problem.
>
> Fourth. No conclusive evidence has been produced to the effect that cancer is hereditary in the accepted sense of the term. My own investigations into the family history of more than 3,000 cancer patients show a lesser degree of incidence than would be expected on the theory of pure chance occurrence. (p 67, 68, ref. 3701)

During the next four decades, it became apparent that dietary theory could also be applied to lung cancer. The reason is not because of discrediting any of the four reasons listed above, but because of the availability of comparative studies on migrants.

Ewing, in the third revision of his treatise on Neoplastic Diseases (2801), discussed the results of Sugiura and Benedict, who attempted to utilize their dietary treatment in human beings suffering from malignant disease with negative results. These authors:

> " ... investigated the influence of natural foods very rich in protein (meat) or very poor in protein (rice), and a diet entirely devoid of protein but containing a large amount of carbohydrate and fat (artificial diet) upon which the susceptibility of animals to cancer implantation. Their results indicate that the susceptibility to tumor inoculation and the growth of such transplants in rats and mice fed with a diet containing meat, milk, or vegetable protein were not altered from the normal. On the other hand, ingestion of a protein-free diet caused marked diminution of tumor growth, but this ration had no specific influence upon tumor susceptibility.
>
> Cholesterol administered subcutaneously in doses of 40 mgm. at intervals of 2 or 3 days was found by Robertson and Burnett to decidedly accelerate the growth of carcinoma in rats. These results were confirmed by Sweet, Carson, White, and Saxon. Tethelin, the active principle of the anterior lobe of the pituitary gland, was found to have a similar effect, and since both these substances contain a hydroxy-benzol group, Robertson and Burnett concluded that the accelerating influence resided in the hydroxy-benzol radical. An increased cholesterol content of the blood has been found in certain cases of cancer by Luden (p 72-74, ref. 2801)

The influence of high cholesterol levels on cancer incidence is discussed in detail under the literature review for the 1960s.

Acute pulmonary irritation. During the 1920's, it was generally assumed that inhalation of irritating vapors caused cellular responses consisting of metapasia, regeneration and malignant disease. Fried conducted histopathologic studies on animal lungs to support his contention that

metaplasia did not originate from alveolar cells but instead from bronchial epithelium (2935). A series of monographs on lung cancer were written by Fried during the next three decades. Unlike Ewing, who wrote on all forms of neoplasms, Fried, a surgeon from Peter Bent Brigham Hospital, specialized on lung cancer. He was a contemporary of Everts Graham, and the surgical skills of the latter were widely publicized, that were both unsuccessful (2211) and successful (see Part Three).

Most lung cancer specialists accepted the proposition that irritation of bronchial mucous membrane preceded the formation of cancer (2936). Several lung cancer cases have been reported in workers exposed to chemicals (2214, 2826, 2828, 2919). However, most instances were acute poisoning following exposure to: chemicals such as benzene (2222, 2829); automobile exhaust gas and fumes (2223, 2224, 2826, 2937); and gases and vapors inside steel mills (2938).

Playfair and Wakeley, in their discussion of etiology of lung cancer, did not favor "chronic inflammatory changes in the bronchial mucosa" as providing the antecedent factor (2317). It would be of interest to know whether any case of chronic bronchitis arising after "gassing" ever developed to primary pulmonary neoplasm. I have been unable to discover any case reports of such an event. The importance of mustard gas exposure was finally answered forty years later and is discussed below under influenza.

Previous chest trauma. Although trauma was for a long time considered a potent factor in the etiology of malignant disease, the case reports relating to lung cancer were rare. Aufrect's report consisted of cases preceded with a fall from a ladder, a falling beam, a blow from a piece of iron, and a bike

have been noted as antecedents of the malignant disease (see Funk, ref. 2016). Tovell reported a teamster who was apparently well until he was struck in the right chest by the tongue of his wagon, developed chest pain and subsequently primary lung cancer (2516). Wood and Walter reported a patient whose great uncle died of cancer of the jaw, and 22 years prior to diagnosis of lung cancer, a "horse fell on him, crushing the left side of the chest," the same side that the lesion later appeared (2116). It was assumed that trauma caused acute inflammation and subsequent fibrosis, both antecedents of pulmonary carcinogenesis. Trauma, per se, did not directly lead to tissue alteration with malignant qualities, but it was only through successive inflammatory changes which resulted in cancer (2722).

Chronic dust diseases of the lungs. During the 1920's, the following chronic lung diseases were already known to cause fibrosis and occasionally lung cancer: pneumoconiosis (2523, 2834), silicosis (2122, 2418, 2836, 2939, 2940), asbestosis (2419, 2724, 2725, 2726, 2835, 2941), and abrasive dust fibrosis (2942, 2943). Some patients with pneumoconiosis also had tuberculosis so that the relative role of dust fibrosis compared to tuberculous process in carcinogenesis continued to be debated (2226, 2324, 2522). Fibrosis alone, without chronic lung dust disease or tuberculosis, but with lung cancer, has been reported to occur (2113).

The lung cancer seen in miners from Schneeberg district of Saxony, Germany, and from Jachymow, Czechoslovakia, were being debated during the 1920's as to whether dust alone or metallic elements such as arsenic, cobalt, or radium, was the carcinogen. The question was resolved during the 1930's.

Pulmonary tuberculosis. During the 1920's, tuberculosis was a significant etiologic factor of lung cancer. This was favored by Ewing (2801) and reiterated by other clinicians (2112, 2212, 2213, 2411, 2514, 2515, 2612, 2613, 2614). The occurrence of pulmonary abscess either tuberculous or non-tuberculous in nature was regarded as a disease process that contributed to "chronic irritation" or "chronic inflammation" and ultimately lung cancer (2325, 2837, 2953). The statistical studies of Pearl indicated that "only rarely does an active and considerable tuberculosis coesist with a malignant neoplasm in the same individual" (2838, 2922). Carlson and Bell explored the suggestion that the two diseases were antagonistic since both rarely co-existed in the same individual (2944). They concluded the following:

> Active tuberculosis is much less frequent in cancerous than in non-cancerous subjects; and cancer is much less common in those with active tuberculosis than in those with no tuberculosis or with healed tuberculosis.
>
> But active tuberculosis is even less frequently associated with heart disease than with cancer; and cancer shows less association with heart disease than with active tuberculosis.
>
> These results do not mean that active tuberculosis inhibits the development of both cancer and heart disease. They are due to the fact that the majority of persons with active tuberculosis have no other major illness and therefore the control (non-cancerous, non-heart disease) must always have a higher percentage of tuberculosis.
>
> We do not find any statistical evidence to support the view that there is an antagonism between cancer and tuberculosis.
>
> The only proper control for the association of active tuberculosis and cancer is the incidence of active tuberculosis in some other disease." (p 134, 135, ref. 2944)

It is important to emphasize that the relationship between pulmonary tuberculosis and cancer continued to be debated for the next three decades.

Influenza pandemic. There were over a score of case reports of lung cancer appearing in patients who have recovered from influenza (2317, see also

Table of Case Reports under Topic B above). Winternitz, Wason and McNamara (2001) wrote a monograph on the Pathology of Influenza:

> It is rare to see such activity on the part of the epithelium as that frequently encountered in influenza. The alveoli may be lined by newly formed cubical cells and mitotic figures in the injured bronchiolar lining occur in abundance. This might lead to the supposition that, if the epithelium were restricted in its path of development, it would pile up to form a typical nest, just as the epithelium at the edge of a healing chronic ulcer of the skin may pile up and extend fairly deep into the tissue. In a number of cases, epithelial proliferation has been so extensive that it could not be differentiated histologically from an invasive, malignant neoplasm. There is no reason to believe that malignancy might not result from the continuous stimulation of the epithelium to proliferate, in the chronic inflammatory process of the lung in influenza, just as chronic infection in the lung of a mouse results in a much higher percentage of spontaneous neoplasms of the respiratory tract in this species than in those animals where chronic pulmonary inflammatory processes are uncommon. It will be interesting, indeed, to see whether, as a late manifestation, there is an increase in the number of now relatively rare epithelial new growths in the respiratory tract of man." p 48, ref. 2001)

In 1960, Beebe examined the health records of the U.S. Army and Veterans Administration to investigate the possible significance of influenza and mustard gas poisoning (6011). Although this publication belongs to another decade, the results are relevant to the 1920's:

> "Two problems in the epidemiology of lung cancer have been attacked on the basis of a mortality study of the U.S. Army veterans of World War I: the 1918 influenza epidemic and war injuries attributed to mustard gas. The basic design is that of a prospective study initiated entirely on the basis of military records created in 1918, aimed at the detection of 3:1 differences between samples of approximately equal size compared as to mortality from lung cancer. Representative rosters of 2,718 white men with mustard-gas injury, 1,855 with pneumonia in 1918, and 2,578 with wounds of the extremities (controls) were created from retired Army records in the St. Louis record depot. Year of birth was confined to 1888-93 inclusive. The original Army clinical records of mustard-gas injury were reviewed according to criteria thought sufficient to insure the validity of the diagnosis and the determination of the responsible agent. The entire roster of 7,151 men was then traced forward

through 1955 on the basis of records of insurance, hospitalization, and disability maintained by the Veterans Administration.

Soon after the study was begun, a report became available by Case and Lea on 1929 British Army pensioners with residuals of mustard-gas injuries received in World War I. Their report suggested that men with mustard-gas injuries had about twice the expected incidence of lung cancer, but only because of an intervening residual in the form of chronic bronchitis. In view of this report the design of the present study was modified to obtain data on VA hospitalizations, outpatient visits, and disability rating for 10 percent of the sample.

The total of 2,441 deaths reported through 1955 was 95 percent of expectation on the basis of age- and time-specific death rates for U.S. white males over this interval. While in the first decade only 71 percent of the expected deaths were found, in the period 1940-55 the proportion of expected deaths was 98 percent. It is believed that the early deficit represents the influence of screening for military service in World War I, and that VA reporting of deaths is substantially complete.

The 3 rosters differ significantly as to gross mortality only in the second decade of the follow-up period, when men on the mustard-gas roster suffered from considerably higher mortality rates. Examination of the deaths by cause revealed that this excess arose primarily from pneumonia and tuberculosis.

The data on mortality from lung cancer are equivocal with respect to the influence of mustard-gas njury, but contain no hint that postinfluenzal pneumonia in the 1918 fall epidemic increased the risk of lung cancer. Observed lung-cancer deaths are 36/2,718, or 1.32 percent, for the mustard-gas roster, and 26/2,578, or 1.01 percent, for the control roster. These percentages do not differ significantly and thus provide but weak support for the view that mustard-gas injury sets the stage for the later development of bronchogenic cancer. However, the study was planned to have good power against a 3:1 ratio but not against a 2:1 ratio, and since Case and Lea reported only a 2:1 ratio in their material, the present finding is not inconsistent with their conclusion. It seemed essential, therefore, to make a supplementary comparison of observed mortality in relation to expectation based on the general U.S. population experience for white males. This can be done for all respiratory cancer and provides a more powerful, if less direct, comparison. In these terms the ratios of observed to expected deaths are 39/26.6, or 1.47 for the mustard-gas roster, 15/18.6, or 0.81, for the pneumonia roster, and 30/26.2, or 1.15, for the control roster. Only the first differs significantly ($P < 0.05$) from unity. Although the study ws not designed on the basis of this approach, because a direct comparison of two sociologically smilar samples, followed up in the same way, seemed distinctly preferable, correspondence between veteran and civilian mortality seems sufficiently close to invest this indirect comparison with more merit than could be assumed for it in the planning stage. As

> originally planned, therefore, the study renders a verdict of "unproved" but the indirect comparison with population values is quite suggestive that an association exists. However, it is not consistent with the view that the increment of risk is large, relative to that existing in the entire control population, the 95 percent confidence interval on the observed ratio of 1.47 being 1.02 to 1.96. The Case and Lea result of 2.07 falls just outside this confidence interval. To the extent that cigarette smoking could be an important source of risk for the control population, for nonsmokers the relative increment of risk associated with a single mustard-gas exposure could, nevertheless, be large." (p 1249, 1250, ref. 6011)

The last quoted statement on cigarette smoking was based on statistical association between cigarette smoking and lung cancer available to Beebe prior to 1960. Although the association between influenza and lung cancer was not casually related based on retrospective epidemiology, one can still argue that Winternitz et al based their opinion on histopathologic observations. The comparison of results between epidemiology and pathology continued for the next four decades without an agreement as to etiologic concepts.

F. Theories of Pulmonary Carcinogenesis

During the 1920's, the prevalent opinion was that lung cancer was the result of an extrinsic or environmental factor as well as intrinsic or inherent susceptibility of the host. The list of hostal factors included previous pulmonary diseases such as tuberculosis, influenza, dust diseases, trauma and chemical irritation. Ewing (280) favored tuberculosis as the most significant cause, but the following authorities who wrote textbooks, monographs and comprehensive review articles did not favor a specific cause: Cabot (3001 and nine other earlier editions); Cecil (2901), Barron (2213), Grove and Kramer (2616), Klotz (2722), Perret (2711), Meyer (2325), Moise (2111), Norris and Landis (2002), Osler (2603), Schuster (2926, 2952), Weller (2912) and Woglum (2601). There is also a 300-paged monograph in French by Huguenin, which is a comprehensive review of the pathological and clinical literature (2802). Portions of this 1928 monograph will need translation into English.

Thomas McCrae, Professor of Medicine at Jefferson Medical College in Philadelphia and co-editor with Osler of Modern Medicine, System of Medicine and Practice of Medicine, summarized the etiology of lung cancer as follows:

> "With reference to the increase in its occurrence there are many suggestions as to possible etiologic factors. Influenza is, of course, suggested, as in many other diseases, but the evidence seems very scanty. The suggestion that it is a result of gassing in war has little support. A result of the increased use of x-rays in the diagnosis of thoracic disease has been given as an explanation. Some attribute the increase to cigarette smoking. If there is anything in this we should see a continued increase, but the evidence seems hardly worthy of belief. Irritation of the bronchi is naturally suggested, as this is a factor in the production of some carcinomas. That dust and smoke may play a part is a tempting

> suggestion, but apparently there is no association between pneumoconiosis and carcinoma shown in autopsy reports. Much more weight should be given to the suggestion that irritating substances of a chemical nature may play a part. You are aware that there is a group of new growths produced by chronic contact with tar products. It has been suggested that the inhalation of particles of tar and oil from roads may play a part in the etiology. In addition, the oxidation products of gasoline may have a similar influence. These suggestions are certainly worthy of careful consideration." (p 12, ref. 2627)

Contrary to the opinion of Harris as expressed in his 1985 SOA Report, Hueper wrote articles in the 1920's that cigarette smoking is an unlikely cause of lung cancer. Instead, Hueper favored the hypothesis that environmental pollutants, especially fossil fuel products and combustion emission, are the cause of lung cancer. The causal relationship was based entirely on supporting animal studies relating to coal tar administered dermally or intratracheally. Experiments on the use of tobacco tar gave equivocal results: no lung cancer by intratracheal route and variable results by dermal route.

There were no epidemiologic studies on the relationship of exposure to fossil fuel products and lung cancer. The causal relationship was based on the observation that a significant number of lung cancer patients were employed as outdoor workers. The subject of <u>Can tar cause pulmonary cancer</u>? was discussed in a 1927 issue of Lancet:

> "An inquest was held on March 5th by the Manchester coroner, Mr. C.W.W. Surridge, on a gas retort worker aged 59, who had been employed by the Manchester Corporation for 26 years. This man was forced to leave his work in March of last year, and subsequently underwent an operation. His duties at the gasworks were to keep the mains clear of tar and to charge up retorts after they had been scraped; he had worked a good deal with tar. The Medical Inspector of Factories, Dr. S.A. Henry, was present, and the corporation was represented. It was stated that the deceased had not worn gloves whilst at work with tar; since he left, gloves had been provided. For the Corporation, it was pointed out that all the men were invited to report any black spots or warts noticed on their bodies. Medical examination was always available free of charge, and

> everything possible was provided to keep the employees clean. Dr. Norman Kletz described the results of the post-mortem examination. A healed scar was found on the scrotum, due to a previous operation for epithelioma, but this disease had apparently been completely eliminated. Death was due to a primary growth in the lung. In reply to the coroner, Dr. Kletz stated that there was no connexion between the previous disease of the scrotum and the lung. He was not in a position to say that the growth in the lung could not have been caused by inhaling the fumes of tar, but he had never heard of such a case. In returning an open verdict, the coroner said that there was no doubt that if epithelioma were treated in its earliest phase a complete cure reulted. Death had resulted from heart failure, due to the pulmonary growth, and he was satisfied that there was no connexion between the cause of death and the earlier disease of the scrotum. Only time and further investigation could show whether a cancerous growth in the lung could be produced by working amidst tar fumes. The coroner added: "Years ago it was not known that there was any connexion between disease of the scrotum and external contact with tar. Now that has been proved to be so, and it may be in days to come that the inhalation of tar fumes will show some connexion with growths in the lungs. It is not sufficiently established as yet, and I propose to return an open verdict." (p 252, ref. 2728)

Two decades later, the high incidence of lung cancer in gas retort workers was reported and a causal relationship was accepted by most authorities. This phenomenon was also seen in other groups of workers exposed to fossil fuel products and combustion emission.

Epidemiology was difficult to apply to the question relating coal tar and lung cancer. The statistical studies on cancer in general were severely criticized by Greenwood, a Professor of Epidemiology and Vital Statistics at the University of London (2818). He questioned the "alleged increase" of cancer:

> "It will be obvious that none of the investigations above briefly described has, taken by itself, essentially changed our scale of values, none has shown that characteristic of the highest class of scientific work. But the cumulative effect of these laborious studies, on the positive side in increasing the precision of our description of the incidence and distribution of fatal cancer, on the negative side in showing the insubstantial character of many popular 'theories' and superstitions, has been appreciable.

> No man dares set limits to the achievements of genius; it might be that a man of the highest order of ability - one who was not only an expert statistician but also master of the very large body of experimental and pathological knowledge relevant to the issue - could, even from the existing imperfect data, deduce conclusions of far-reaching importance. Such men, however, are rare and no man of genius has yet turned his attention to this branch of the subject, which in the public mind tends to be associated with the facile generalizations of journalists and other enthusiastic but uncritical amateurs rather than with serious research. It is probable that by the gradual improvement in accuracy and completeness of the medical statistics of all nations we can best prepare the way for a really illuminating survey of the cancer problem. One of the advantages of the awakening of public interest in this matter is that in almost all countries - as the abstracts in this Review testify - there are signs of improvement in the official records. It cannot, however, be said that at present much more can be hoped from the statistical method than an impartial study of strictly defined problems. The time is still distant when the data of all civilized countries and all subdivisions of these countries will be strictly comparable." (p 106, ref. 2818)

The "man of the highest order of ability" was selected fifty years later to be Greenwood himself, as discussed in the next subsection. For five decades starting with the 1920's, there has been continuous discussion that fossil fuel products and combustion emission are the most likely environmental factor causing lung cancer in a susceptible host.

BIBLIOGRAPHY

PART II, SUBSECTION II - THE 1920's

Note: The four digit numerical system was described in the Bibliography of Part One (page 18). The 2000 series include publications from 1920 to 1929: thus, 2000's were published in 1920, 2100's in 1921, 2200's in 1922, 2300's in 1923, and so on until 2900's in 1929. Symbols used on cited publications are as follows:

[] = Harris' SOA report, DTH exhibits, and ERR
"P" = Secondary citations in Harris' representative key articles
"DMA" = Citations in my 1986 Critique to replace mislaid copies
"WHM" = Articles derived from 1967 Wynder and Hoffman Monograph
"SGR" = Cancer references in the 1964 Surgeon General's Report
"TOP" = Transcript of Proceedings
"ERR" = Expert's Response to Requests (for additional information)
"*" = Articles to be submitted at the end of project
"+" = German or French articles in need of English translation

Entries without brackets [] were derived from manual searches of medical indices as explained in page 11.

1920 Books and Monographs

2001 Winternitz MC, Wason IM, McNamara FP: The pathology of influenza. New Haven: Yale University Press, 39-61, 1920. [Cited P6, P180, P181, P214; SGR 371; WHM 249]

2002 Norris GW, Landis HRM: Diseases of the chest and the principles of physical diagnosis. Philadelphia: WB Saunders Co., Second Edition, Revised, 542-556, 1920.

1920 Periodicals

2011 McDonnell PJ, Maxwell ES: Endothelioma of the pleura. JAMA 74: 168-170, 1920.

2012 Vallee A: A case of endothelioma of the pleura with multiple metastasis. Canad Med Assoc J 10: 268-269, 1920.

2013 Gordon AK: Note on a case of primary diffuse alveolar carcinoma of the lung. Lancet 2: 501, 1920.

2014 Hogner R: Tobacco poisoning without using tobacco. Am Med 26: 111-112, 1920.

2015 Baumberger JP, Martin EG: Fatigue and efficiency of smokers in a strenuous mental occupation. J Ind Hyg 2: 207-214, 1920.

2016 Funk EH: Malignant disease of the lung. Med Clin NA 3: 1197-1222, 1920. [DMA 516]

1921 Periodicals

2111 Moise TS: Primary carcinoma of the lungs. Arch Int Med 28: 733-772, 1921. [cited P181, P189]

2112 Christie AC: The diagnosis of primary tumors of the lung. Am J Roentgenol 8: 97-103, 1921.

2113 Robey WH: Malignant disease of the lung. Med Clin NA 4: 1811-1837, 1921. [DMA 510]

2114 Pritchard JS: An unusual case of pulmonary neoplasm. Am J Roentgenol 8: 555-559, 1921.

2115 Carman RD: Primary cancer of the lung from the roentgenologic viewpoint. Med Clin NA 5: 307-353, 1921. [cited P181]

2116 Wood EA, Walter AL: Primary mesothelioma of the pleura - with report of a case. J Missouri Med Assoc 18: 277-281, 1921.

2117 Friedman GA: Carcinoma of the lung, report of a case. Med Rec 100: 980-981, 1921.

2118 Blumgarten AS: Diagnosis of primary lung tumors. Am J Med Sci 162: 376-385, 1921. [DMA 511]

2119 Baumberger JP, Perry EE, Martin EG: An output study of users and non-users of tobacco in a strenuous physical occupation. J Ind Hyg 3: 1-10, 1921. [cited P398]

2120 Holmes PK: Tobacco in its relationships to public health. Am J Public Health 11: 793-795, 1921.

2121 Brigham RO: Heart failure and tobacco as an etiological factor. Ohio State Med J 17: 226-228, 1921.

2122 Middleton EL: A study of pulmonary silicosis. J Ind Hyg 2: 433-449, 1921.

2123 Sugiura K, Noyes HM, Falk KG: The influence upon the growth of transplanted Flexner-Jobling rat carcinoma of hydrogen ions and of various salts in different concentrations. J Canc Res 6: 285-303. 1921. [cited P264]

2124 Eastwood EH, Martin JP: A case of primary tumour of the pleura. Lancet 2: 172-174, 1921.

1922 Periodicals

2211 Sale L: Tumors of the mediastinum: 3 cases. Med Clin NA 6: 189-196, 1922. [cited P189]

2212 Rizer RI, Habein HC: Primary carcinoma of the lung. Minnesota Med 5: 352-356, 1922.

2213 Barron M: Carcinoma of the lung: a study of its incidence, pathology and relative importance, with a report of thirteen cases studied at necropsy. Arch Surg 4: 624-660, 1922. [cited P181, P189]

2214 Bridges WO, Moser RA: Primary carcinoma of the lung with report of cases. Nebraska Med J 7: 377-381, 1922.

2215 Dana HW, McIntosh R: Obstruction of superior vena cava by primary carcinoma of lung, pathological report. Am J Med Sc 163: 411-425, 1922.

2216 Wohl MG: Pathology of primary carcinoma of the lung. Nebraska Med J 7: 381-383, 1922.

2217 Haynes GS, Gaskell JF: A case of primary carcinoma of the lung. Brit Med J 1: 222-223, 1922.

2218 Pinchin AJS: A case of carcinoma of the lung of unusual duration. Lancet 1: 792-793, 1922.

2219 Armstrong HE: Carbonic oxide in tobacco smoke. Brit Med J 1: 992-993, 1922. [SOA 7; cited P38, P74]

2220 Passey RD: Experimental soot cancer. Brit Med J 1: 1112-1113, 1922. [SOA 184; cited P39; SGR 266; WHM 110, etc.]

2221 Leitch A: Paraffin cancer and its experimental production. Brit Med J 2: 1104-1106, 1922. [SGR 203; DMA 622]

2222 Hamilton A: The growing menace of benzene (benzol) poisoning in American industry. JAMA 78: 627-630, 1922.

2223 Sayers RR: Physiological effects of exposure to low concentrations of carbon monoxide. Pub Health Rep 37: 1127-1142, 1922. [cited P159, P398]

2224 Henderson Y, Haggard HW, Teague MC, Prince AL, Wunderlich RM: Physiological effects of automobile exhaust gas and standards of ventilation for brief exposures. J Ind Hyg 14: 79-92, 137-146, 1922. [cited P159, P398]

2225 Drinker CK: Modern views upon the development of lung fibrosis. J Ind Hyg 3: 295-303, 1922.

2226 Landis HRM: Pneumokoniosis and tuberculosis, with special reference to both diseases in potters. Am Rev Tuberc 6: 766-771, 1922.

1923 Periodicals

2311+ Hüper W: Uber die histologischen Veränderungen im menschlichen Gewebe nach Injektion von Parraffin. Frankfurter Zeitschrift fur Pathologies 29: 268-286, 1923.

2312 Ferguson R: Primary carcinoma of both lungs, case reports. Southwestern Med 7: 247-248, 1923.

2313 Schroeder JH: Massive neoplasm of the lung with paralysis of the diaphragm. New York Med J 118: 628-630, 1923. [cited P189]

2314 Maclachlan WWG: The clinical manifestations of primary cancer of lung. Atlantic Med J 26: 655-659, 1923.

2315 Fontaine BW: Pulmonary fibrosis, report of case. JAMA 80: 1129-1132, 1923.

2316 Major RH: Primary carcinoma of the lung. J Kansas Med Soc 23: 97-99, 1923.

2317 Playfair K, Wakeley CPG: Primary carcinoma of the lung. A discussion of its incidence and diagnosis. Brit J Surg 11: 203-217, 1923.

2318 Gibson HJC, Findlay GM: A case of primary carcinoma of the lung. Lancet 1: 21-22, 1923.

2319 Folson SA: A case of primary carcinoma of the lung. J Med Assoc Georgia 12: 406-410, 1923.

2320 Baumberger JP: The carbon monoxide content of tobacco smoke and its absorption on inhalation. J Pharmacol Exp Ther 21: 23-34, 1923. [SOA 13, ERR P13; cited P74; WHM 78]

2321 Kimura N: Artificial production of a cancer in the lungs following the intrabronchial insufflation of coal-tar. Japan Med World 3: 45-47, 1923. [cited P131, P181]

2322 Leitch A: The experimental injury into the causes of cancer. Brit Med J 2: 1-7, 1923. [DMA 409]

2323 Baumberger JP: The nicotine content of tobacco smoke. J Pharmacol Exp Ther 21: 35-46, 1923.

2324 Nicholson BS: The dusted lung with special reference to the inhalation of silica dust (SiO2) and its relation to pulmonary tuberculosis. J Ind Hyg 5: 220-242, 1923.

2325 Meyer W: Observations on lung suppuration and its treatment. A brief review of personal experiences and clinical impressions obtained within the last twelve years. Arch Surg 6: 361-425, 1923. [cited P180, P181]

2326+ Roesch H: Drei verschiedene Carcinome bei einem Parafiinarbeiter. Virchows Archiv A Pathol Anat Histol 245: 1-8, 1923.

1924 Periodicals

2411 Bronfin ID: Pitfalls in diagnosis of primary carcinoma of the lung. Colorado Med 21: 155-163, 1924. [cited P189]

2412 Zeckwer IT: Mesothelioma of the pleura. Arch Int Med 34: 191-205, 1924.

2413 Lilienthal H: Malignant tumor of the lung: necessity for early operation. Arch Surg 8: 308-316, 1924. [DMA 513]

2414 Pancoast HK: Importance of careful roentgenray investigations of apical chest tumors. JAMA 83: 1407-1411, 1924.

2415 Kennaway EL: On cancer-producing tars and tar-fractions. J Ind Hyg 5: 462-488, 1924. [cited P45, P129, P264]

2416 Kennaway EL: The formation of a cancer-producing substance from isoprene (2-methyl-butadiene). J Pathol Bacteriol 27: 233-238, 1924. [cited P129, P264; WHM 145, etc.]

2417 Leitch A: Mule-spinners' cancer and mineral oils. Brit Med J 2: 941-943, 1924. [cited P129; SGR 204]

2418 Britton JA: Silicosis: a modern factory health hazard. J Ind Hyg 6: 199-202, 1924.

2419 Cooke WE: Fibrosis of the lungs due to the inhalation of asbestos dust. Brit Med J 2: 147, 1924.

2420+ Oppenheim M: Ein noch nicht beschriebenes berufliches Kennzeiches an der Haut der Schuhmacher. Arch Dermatol Syph 147: 359-361, 1924.

1925 Books and Monographs

2501 Hamilton A: Industrial poisons in the United States. New York: The Macmillan Co. 510 pages, 1925. [cited P159, P181, P398]

1925 Periodicals

2511 Eloesser L: Primary tumors of the lung. Arch Surg 10: 455-468, 1925. [cited P181]

2512 Stern S: The treatment of lung and mediastinal neoplasms by high voltage roentgen therapy. Am J Roentgenol 14: 8-14, 1925. [cited P181, P189]

2513 Moses HM: Primary carcinoma of the lung. Am J Med Sc 120: 102-118, 1925. [cited P181, P214; DMA 514]

2514 Greenberg D: Pulmonary neoplasm: a clinical study of three cases. Am J Med Sc 169: 648-655, 1925.

2515 Harrell CL: Malignancy of the lung from the clinical standpoint. Virginia Med Month 3: 304-309, 1925.

2516 Tovell HM: X-ray findings in primary carcinoma of the lung. Canad Med Assoc J 15: 485-488, 1925. [cited P181]

2517 Kennaway EL: Experiments on cancer-producing substances. Brit Med J 2: 1-4, 1925. [SOA P129; cited P81]

2518 Passey RD, Carter-Braine J: Experimental soot cancer. J Pathol Bacteriol 28: 133-144, 1925. [cited P39]

2519 Passey RD, Woodhouse JL: The influence of the fat-soluble accessory food factor upon initiation of soot cancer in mice. J Pathol Bacteriol 28: 144-145, 1925.

2520 Murphy JB, Sturm E: Primary lung tumors in mice following the cutaneous application of coal tar. J Exptl Med 42: 693-700, 1925. [cited P38, P39, P131, P158, P181; SGR 251; WHM 382]

2521 Cowdry EV: Studies on the etiology of jagziekte. II. Origin of the epithelial proliferations, and the subsequent changes. J Exptl Med 42: 335-345, 1925.

2522 Bledsoe NC: Lung conditions found in our industrial work other than tuberculosis and silicosis. Southwestern Med 9: 297-300, 1925.

2523 Oliver T: Some dusty occupations and their effects upon the lungs. J Sanit Inst 46: 224-230, 1925.

2524 Kennaway EL: The anatomical distribution of the occupational cancers. J Ind Hug 7: 69-93, 1925.

1926 Books and Monographs

2601 Woglom WH: Experimental tar cancer. Arch Pathol Lab Med 2: 533-575, 709-752, 1926.

2602 Evans E: A psychological study of cancer. New York: Dodd, Mead & Co., 1926.

2603 Osler W: The principles and practice of medicine, 10th Edition. New York: D Appleton & Co, 663-665, 684-685, 1926.

1926 Periodicals

2611 Green HW: Cancer mortality. Am J Pub Health 16: 605-609, 1926. [cited P214]

2612 Atkinson CE: Pulmonary neoplasms. Am Rev Tuberc 14: 556-566, 1926.

2613 Brunn H: Primary carcinoma of the lung. Report of two operative cases. Arch Surg 12: 406-439, 1926.

2614 Blackwood JD, Jr: Malignant disease of the lungs with report of case. US Nav Med Bull 24: 885-892, 1926.

2615 Perry MW: Primary carcinoma of the lung. Int Clin 3: 194-200, 1926.

2616 Grove JS, Kramer SE: Primary carcinoma of the lung. A clinical and pathologic study from the Cook County Hospital, with a report of 21 necropsies and 3 biopsies. Am J Med Sc. 151: 250-282, 1926. [cited P115, P181, P189, P334]

2617 Gaarde FW: Clinical differentiation of cases with abnormal x-ray shadows in the mediastinum. Med Clin NA 8: 1234-1236, 1926.

2618 Eshleman CL: An intrathoracic growth with simulating aneurysm. Med Clin NA 9: 1109-1114, 1926. [cited P189]

2619 Lichty JA, Wright FR, Baumgartner EA: Primary cancer of the lungs. A clinical report of seventeen cases. JAMA 87: 144-151, 1926. [cited P115, P145, P189; DMA 505]

2620 Fishberg M: Diagnosis of pulmonary neoplasm. Arch Int Med 37: 745-772, 1926. [cited P 181, P189]

2621 Lenk R: Differential diagnosis between tumors and tuberculosis of the lung. Arch Phys Ther 7: 529-542, 1926.

2622 Bel GS: Primary carcinoma of the lung. Med Clin NA 4: 887-893, 1926. [cited P189]

2623 Hueper W: Primary gelatinous cylindrical cell carcinoma of the lungs. Am J Pathol 2: 81-90, 1926. [cited P181]

2624 Editorial: The recent increase in pulmonary cancer. JAMA 86: 486-487, 1926. [cited P189]

2625 Fujimaki Y: Formation of gastric carcinoma in albino rats fed on deficient diets. J Canc Res 10: 469-477, 1926.

2626 Lynch CJ: Studies on the relation between tumor susceptibility and heredity. III. Spontaneous tumors of the lung in mice. J Exp Med 43: 339-355, 1926.

2627 McCrae T: Carcinoma of the bronchus: Hemiplegia. A diagnostic study. Med Clin NA 10: 1-15, 1926.

2628 Emerson H, Hughes HE: Death rates of male white physicians in the United States, by age and cause. Am J Publ Health 16: 1088-1093, 1926.

1927 Books and Monographs

2701 Marwood FT: What is the root cause of cancer? Is it the excessive consumption of common salt, salted foods and salt compounds? London: John Bale, Sons & Danielsson, Ltd., p 1-31, 1927. [cited P152]

1927 Periodicals

2711 Perret JM: Primary intra-thoracic malignancy. New Orleans Med Surg J 80: 213-228, 1927. [SOA 189, key P189, DTH exhibit 84, cited P145]

2712 Wells HG: Cancer statistics as they appear to a pathologist. JAMA 88: 399-402; 476-482, 1927.

2713 Sherman J: Primary carcinoma of the lung. California West Med 26: 40-45, 1927.

2714 Hyde TL, Holmes GW: The roentgenological aspects of primary tumors of the lung. Am J Roentgenol 18: 235-243, 1927. [cited P181]

2715 Schultz SR: A contribution to the study of primary carcinoma of the lung. Arch Clin Canc Res 3: 107-118, 1927.

2716 Rubenstone AI, Schwartz M: Primary intrathoracic neoplasms: an analysis of eleven cases. Med J Rec 126: 719-722, 1927. [cited P181]

2717 Illingworth HT: Carcinoma of the right lung. Med J Australia 1: 611-613, 1927.

2718 Sison AG, Monserrat C: Primary malignant tumors of the lung, their incidence in the Philippines, and their most common clinical manifestation. J Philippine Med Assoc 7: 422-430, 1927. [cited P181, P214]

2719 Tylecote FE: Cancer of the lung. Lancet 2: 256-257, 1927. [SOA 189, key P271, DTH exhibit 85; cited P90, P115, P181, P289]

2720 Helwig FC: Influence of tobacco and other extracts on the epithelial cell. J Kansas Med Soc 27: 37-40, 1927. [cited P159, P398; DMA 411]

2721 Duguid JB: The incidence of intrathoracic tumours in Manchester. Lancet 2: 111-125, 1927. [cited P115, P181, P271]

2722 Klotz O: Cancer of the lung; with a report upon twenty-four cases. Canad Med Assoc J 17Z: 989-996, 1927. [cited P181]

2723 Baumberger JP: The amount of smoke produced from tobacco and its absorption in smoking as determined by electrical precipitation. J Pharmacol Exp Ther 21: 47-57, 1927.

2724 Cooke WE, Hill CF: XII. Pneumokoniosis due to asbestos dust. J Roy Micr Soc 47: 232-238, 1927.

2725 Cooke WE: Pulmonary asbestosis. Brit Med J 2: 1024-1025, 1927.

2726 McDonald S: Histology of pulmonary asbestosis. Brit Med J 2: 1025-1026, 1927.

2727 Robertson J: An inquiry in regard to the cause of spinners' scrotal cancer. J Ind Hyg 9: 217-238, 1927.

2728 Anon: Can tar cause pulmonary cancer? Lancet 1: 582, 1927.

2729 Lynch CJ: Studies on the relation between tumor susceptibility and heredity. IV. The inheritance of susceptibility to tar-induced tumors in the lungs of mice. J Exp Med 46: 917-733, 1927. [SGR 226]

2730* Lombard HL, Doering CR: Cancer studies in Massachusetts. 1. The relationship between cancer and density of population in Massachusetts. Proc Nat Acad Sci 13: 72--735, 1927.

1928 Books and Monographs

2801 Ewing J: Neoplastic diseases - a treatise on tumors. Third Edition. Philadelphia: WB Saunders Co., pp 851-863, 1082, 1928.

2802+ Huguenin R: Le cancer primitif du poumon; etude anatomo-clinique. Paris: Mason & Cie, 1928. [cited P181]

1928 Periodicals

2811 Williamson CS: Primary carcinoma of the lung. Two cases. Med Clin NA 12: 1-20, 1928.

2812 Taub SJ: Primary bronchogenic carcinoma of the lung. Med Clin NA 12: 279-284, 1928.

2813 Johnson GC, Hurst WR: Report of case of cancer of the lung. J Indiana Med Assoc 21: 285-287, 1928.

2814 Stivelman BP: The roentgen ray in the diagnosis of primary pulmonary neoplasm. JAMA 91: 1690-1694, 1928. [cited P181]

2815 Reisner D: Intrabronchial polypoid adenoma - report of a case. Arch Surg 16: 1201-1213, 1928.

2816 Brewster HD: Primary carcinoma of the lung. US Vet Bureau Med Bull 4: 259-262, 1928.

2817 Cooper DA: Primary carcinoma of the lung. Med Clin NA 12: 1109-1120, 1928.

2818 Greenwood M: A review of recent statistical studies of cancer problems. Canc Rev 3: 97-107, 1928.

2819 MacMillan CW: Report of a case of primary carcinoma of the lung. Canad Med Assoc J 18: 186-187, 1928.

2820 Shennan T: Tumours of mediastinum and lung. J Pathol Bacteriol 31: 365-402, 1928. [cited P181]

2821 Vinson PP, Moersch HJ, Kirklin R: Value of bronchoscopy in diagnosis of malignant conditions of the lung. JAMA 91: 1439-1443, 1928.

2822 Appleton JLT, Lehmer E: The effect of cigarette smoking on the number of bacteria removable in mouth rinsings. Dent Cosmos 70: 111-1121, 1928. [SOA 5]

2823 Hueper WC: Agranulocytosis (Schultz) and the agranulocytic symptom complex. Arch Int Med 42: 893-900, 1928.

2824 Henry SA: Mule spinners' cancer: the time necessary for its production. J Hyg 28: 100-103, 1928. [cited P131]

2825 Kennaway EL, Sampson B: Tumours of the skin and mammary gland caused by pyrogenous products of cholesterol. J Pathol Bacteriol 31: 609-612, 1928. [SOA 133; cited P81]

2826 Smith RE: The etiology of primary lung carcinoma: an experimental and clinical investigation. J Canc Res 12: 134-142, 1928. [cited P164, P181]

2827 Helwig FC: The growth-producing effects of extracts of tobacco on mice. JAMA 91: 150-151, 1928. [cited P81, P244, P245, P264, P291; WHM 256; DMA 412]

2828 Heaton TG: Two cases of cancer of the lung. Canad Med Assoc J 19: 698-701, 1928.

2829 Smyth HF, Smyth HF, Jr: Spray painting hazards as determined by the Pennsylvania and the National Safety Council surveys. J Ind Hyg 10: 163-214, 1928.

2830 Hill L: The ciliary movement of the trachea studied in vitro - a measure of toxicity. Lancet 2: 802-805, 1928.

2831 Wills HS, Brutsaert P: Tumor-like structures in the lungs of guinea pigs artificially exposed to silica dust. Am Rev Tuberc 17: 268-278, 1928.

2832+ Maisin J, Francois DA: Influence du regime alimentaire sur l'eclosion et l'evolution du cancer du goudron. Ann Med 24: 455-467, 1928.

2833* Lombard HL, Doering CR: Cancer studies in Massachusetts. 2. Habits, characteristics and environment of individuals with and without cancer. New Eng J Med 198: 481-487, 1928. [SOA 152, key P152, DTH exhibit 34, TP 1539-1543; cited P208; SGR 221]

2834 Seiler HE: A case of pneumoconiosis - result of the inhalation of asbestos dust. Brit Med J 2: 982, 1928.

2835 Simson FW: Pulmonary asbestosis in South Africa. Brit Med J 1: 885-887, 1928.

2836 Badham C: Notes on a fine type of fibrous penumonokoniosis produced by silicates and other minerals. Stud Ind Hyg (13): 102-110, 1928.

2837 Graham EA: Remarks on carcinoma of the lung. South Med J 21: 199-202, 1928.

2838 Pearl R: Cancer from the viewpoint of the human biologist. Int Clin 3: 53-77, 1928. [cited P181]

2839* Bigelow GH, Lombard HL: Experience with the program of cancer control in Massachusetts. Am J Pub Health 18: 413-420, 1928. [cited P152]

2840 Kirklin BR, Paterson R: The roentgenologic manifestations of primary carcinoma of the lung. I. Parenchymal type. Am J Roentgenol 19: 20-27, 1928.

1929 Books and Monographs

2901 Cecil RL: A text-book of medicine by American Authors. Philadelphia: WB Saunders Co., pp 823-825, 1929.

1929 Periodicals

2911 Hoffman FL: Cancer of the lungs. Am Rev Tuberc 19: 392-406, 1929. [SOA 115, key P115; cited P90, P18;1, P289]

2912 Weller CV: Pathology of primary carcinoma of the lung. Arch Pathol 7: 478-519, 1929. [cited P181, P214, P278]

2913 Mills RG, Mumey N: Bronchogenic squamous cell carcinoma. Report of a case associated with pleural effusion and pulmonary osteo-arthropathy, with features that simulated infection by endameba histolytica. Arch Int Med 43: 516-532, 1929.

2914 Snider SH, Wood LE: Primary bronchogenic carcinoma - clinical features. J Kansas Med Soc 30: 374-377, 1929.

2915 Leitch CG: Primary carcinoma of lung. J Kansas Med Soc 30: 160-164, 1929.

2916 Feldman M: The diagnosis of metastatic neoplasm of the lungs by the roentgen-ray. Bull Sch Med Univ Maryland 15: 92-102, 1929.

2917 Twort CC, Fulton JD: Experiments on the nature of the carcinogenic agents in mineral oil. J Pathol Bacteriol 32: 149-161, 1929.

2918 Gray SH, Cordonnier J: Early carcinoma of the lung. Arch Surg 19: 1618-1626, 1929.

2919 Hickey PM: Pulmonary neoplasms. J Missouri Med Assoc 26: 440-444, 1929.

2920 Meyer W: Primary cancer of the lung. Arch Surg 18: 307-314, 1929.

2921 Lilienthal H: Primary carcinoma of the lung - lobectomy. Surg Clin NA 9: 551-561, 1929.

2922 Pearl R: Cancer and tuberculosis. Am J Hyg 9: 97-159, 1929. [cited P18]

2923 Ravdin IS: Primary lung carcinoma. Am J Surg 6: 337-341, 1929. [cited P181]

2924 Weiss E: The differential diagnosis of primary and secondary carcinoma of the bronchi. Am J Med Sci 117: 487-494, 1929.

2925 Hunt TC: Pulmonary neoplasms - a report of twenty-six cases. Lancet 1: 759-762, 1929.

2926 Schuster NH: Primary carcinoma of the lung. J State Med 37: 278-288, 1929.

2927 Simpson SL: Primary carcinoma of the lung. Quart J Med 22: 413-449, 1929. [cited P181, P334]

2928 Bogen E: The composition of cigarets and cigaret smoke. JAMA 93: 1110-1114, 1929. [SOA 25; key P25; cited P26, P28, P74, P116, P159, P398]

2929 Vickery HB, Pucher GW: The determination of ammonia and amide nitrogen in tobacco by the use of permutit. J Biol Chem 83: 1-10, 1929. [cited P30]

2930 Johnson WM: Tobacco smoking - a clinical study. JAMA 93: 665-667, 1929. [cited P26, P28, P159, P244, P398]

2931* + Linckint F: Tabak und Tabakrauch als ätiologischer Faktor des Carcinoms. Ztschr f Krebsforsch 30: 349-365, 1929. [SOA 145, key P145; cited P28, P81, P116, P181]

2932 Hirsch IS: The roentgen diagnosis of malignant neoplasms of the lung. Radiology 9: 470-496, 1929. [cited P181]

2933 Hueper WC: Carcinoma of the lung. Illinois Med J 56: 296-304, 1929.

2934 Woglom WH, Herly L: The carcinogenic activity of tar in various dilutions. J Canc Res 13: 367-372, 1929. [cited P28]

2935* Fried BM: Primary carcinoma of the lungs. III. Histogenesis and metaplasia of bronchial epithelium. Arch Pathol 8: 46-67, 1929.

2936 Miller JA, Jones OR: Primary carcinoma of the lungs. Trans Natl Tuberc Assoc 25: 115-119, 1929.

2937 Sayers RR, Yant WP, Levy E, Fulton WB: Effect of repeated daily exposure of several hours to small amounts of automobile exhaust gas. Pub Health Bull (186): 1-57, 1929.

2938 Farmer CJ, Crittenden PJ: A study of the carbon monoxide content of the blood of steel mill operatives. J Ind Hug 11: 329-335, 1929.

2939 Middleton EL: The present position of silicosis in industry in Britain. Brit Med J 2: 485-489, 1929.

2940 Sayres ER, Hayhurst ER, Lanza AJ: Satus of silicosis. Am J Pub Health 19: 635-640, 1929.

2941 Haddow AC: Clinical aspects of pulmonary asbestosis. Brit Med J ;2: 580-581, 1929.

2942 Clark WI: The dust hazard in the abrasive industry: second study. J Ind Hyg 11: 92-96, 1929.

2943 Bridge JC, Cooke WE, Haddow AC, et al: 97th annual meeting of the British Medical Association (Section on Ocupational Diseases). Brit Med J 2: 203-204, 1929.

2944 Carlson HA, Bell ET: A statistical study of the occurrence of cancer and tuberculosis in 11,195 postmortem examinations. J Canc Res 13: 126-135, 1929.

2945 Sydenstricker E: Economic status and the incidence of illness. Pub Health Rep 44: 1821-1833, 1929. [cited Harris' 1987 article]

2946 Kirklin BR: The roentgen ray in the diagnosis of primary carcinoma of the lung. California West Med 31: 247-250, 1929.

2947 Kirklin BR, Vinson PP: Primary carcinoma of the lung. Surg Gynecol Obstet 48: 191-199, 1929.

2948+ Shabad LM: Studien über primäre Lungengeschwülste bei Mäusen und ihr Verhalten zum Steinkohlenteer,als cancerogenem Faktor. Zeitschrift f Krebsforschung 30: 24-59, 1929.

2949+ Steinbrück C: Künstliche Krebserzeugung durch Druckerschwärze. Berliner Tierarztliche Wochenschrift 45: 525-527, 1929.

2950 Weller CV: The pathology of certain signs and symptoms in primary carcinoma of the lung: illustrative cases. Ann Int Med 2: 725-746, 1929.

2951* Lombard HL, Doering CR: Cancer studies in Massachusetts. 3. Cancer mortality in nativity groups. J Prev Med 3: 343-361, 1929.

2952 Schuster NH: Aetiology and pathology of primary lung tumours. J Pathol Bacteriol 32: 799-811, 1929.

2953 Fenger EPK, Petter CK: Active tuberculosis and cancer in the same individual. Minnesota Med 12: 271-275, 1929.

1930 to 1989 Books and Monographs

3001* Cabot RC: Physical diagnosis, Tenth Edition. New York: William Wood & Co., 1930.

3701 Hoffman FL: Cancer and diet. Baltimore: Williams & Wilkins Co., 1937.

6201* James G, Rosenthal T, Editors: Tobacco and health. Springfield: Charles C Thomas, 1962.

8501 Kevles DJ: In the name of eugenics - genetics and the uses of human heredity. New York: Alfred A. Knopf, 1985. [ERR 24]

1930 to 1989 Periodicals

6011* Beebe GW: Lunc cancer in World War I veterans: possible relation to mustard-gas injury and 1918 influenza epidemic. J Nat Canc Inst 25: 1231-1252, 1960. [SGR 20]

7511 Kipling MD, Waldron HA: Percivall Pott and cancer scroti. Brit J Ind Med 32: 244-250, 1975.

8711* DeLuchi MA et al: A comparative analysis of future transportation fuels. Inst Transport Studies, Univ California, Berkely, 1987.

8812* Anon: Auto overuses - dirty air. Nat Assoc Railroad Passengers. News, Feb. 1988.

8902 Brown LR et al: State of the World - 1989. A Worldwide Institute Report on progress toward a sustainable society. New York: WW Norton & Co., 1989.

8912 Sancton TA: Planet of the year. Time Magazine, January 2, 1989.

Biographical Data of Eleven Selected Physicians

From (6802) Debus AG, Editor: World Who's Who in Science - from antiquity to the present. Chicago: Marquis Co., 1968.

Armstrong, Henry Edward, p 63

Barron, Moses, p 117

Emerson, Haven, p 523

Hamilton, Alice, p 743

Kennaway, Sir Ernest Laurence, p 922

Leitch, Archibald, p 1022

Lilienthal, Howard, p 1044

McCrae, Thomas, p 141

Meyer, Willy, p 1171

Osler, William, p 1291-2

Ravdin, Isidor Schwaner, p 1398

Note: There are no biographical datas of over 20 authors of publications that were quoted in Part Two, Subsection II - the 1920's.

2062855186

ARMSTRONG, Henry Edward, English chemist; b. London, Eng., May 6, 1848; s. Richard and Mary Ann (Biddle) A.; student Royal Coll. Chemistry, 1865, 67; Ph.D., Leipzig, Germany, 1870; LL.D., St. Andrews U., Scotland; D.Sc., Madrid, also Melbourne; m. Frances Louisa Lavers, 1877; 4 sons, 3 daus. Tchr., St. Bartholomew's Hosp., 1870-72; prof. chemistry London Instn., 1871-84, London Inst., 1884-1913; prof. Central Tech. Coll. City and Guilds London Inst., from 1879; asso. with Rothamsted Research Sta. Recipient Davy medal, 1911; Messel medal Soc. Chem. Industry, 1922; Albert medal Royal Soc. Arts, 1930; Horace Brown medal Inst. Brewing. Fellow Royal Society, 1876; member of the Chemical Society (president 1893-95), British Association. Author: An Introduction to Organic Chemistry, 1874, 80; Teaching of the Scientific Method, 1903; The Art and Principles of Chemistry, 1927; (with C. E. Groves) rev. edit. Organic Chemistry (Book III of W. A. Miller's Elements of Chemistry), 1880. Recognized importance of periodic law; called chem. change reversed electrolysis; proposed quinonoid theory of color, benzene substitution, also centric formula of benzene; adopted idea of residual affinities; main supporter (with Mendeléeff) Chem. theory of solution; developed hydroxylation theory; proposed modern systematic organic names at Geneva Congress, 1892; suggested name catalyst instead of contact substance; investigated enzymes, naphthalene, camphor, crystallography. Died London, July 13, 1937.

BARRON, Moses, physician, pathologist; b. Kovno, Russia, Nov. 8, 1883; B.S., U. Minn., 1910, M.D., 1911; m. 1919; 4 children. Came to U. S., naturalized, 1896. Demonstrator pathology, bacteriology U. Minn., 1912-13, instr. pathology, 1913-16, asst. prof., 1916-25, asso. prof., 1925-33, prof., 1933-52, prof. emeritus, 1952—, staff, Univ. Hosp., 1924-26; also pvt. practice medicine. Dir. pathology lab. City Hosp., Mpls., 1913-14, City and County Hosp., St. Paul, 1914-17; staff St. Mary's Hosp., 1921—, Asbury Hosp., 1926—, City Hosp., 1927-52. Fellow A.C.P.; mem. A.M.A., Central Soc. Clin. Research, Minn. Acad. Medicine, Diabetes Assn. Work on relation of islets of Langerhans to diabetes, 1920 (led to discovery of insulin), carcinoma of lung, diseases of pancreas, Hodgkins disease, hepatomegaly, splenomegaly.

2062855187

2062855188

EMERSON, Haven, Am. physician; b. N.Y.C., Oct. 19, 1874; s. J. Haven and Susan (Tompkins) E.; A.B., Harvard, 1896; A.M., Columbia, 1899, D.Sc., 1934; M.D., Columbia Coll. Phys. and Surg. 1899; m. Grace Parrish, June 15, 1901; children—Ethel, Robert, J. Haven, Ruth, Ralph. Practiced in N.Y.C., 1899-1957; asst. in physiology and medicine Coll. Phys. and Surg., 1902-14; asst. vis. physician Bellevue Hosp., 1906-14; pres. Bd. Health, and commr. Dept. Health City N.Y., 1915-17; prof. preventive medicine Cornell U.; dir. Cleve. Hosp. and Health pub. Survey, 1919-20; prof. pub health adminstrn. Columbia, 1922-40, emeritus, 1940-57. Dir. health and hosp. surveys in many cities of U. S., also Athens, Greece, 1921-31; dir. N.Y. Hosp Survey, 1935-37. Mem. Board of Health, N.Y.C., 1937-57. Recipient Lasker award, 1949, Gold Heart award Am. Heart Assn., 1953. Mem. Am. Pub. Health Assn. (pres. 1933-34, Sedgwick medal 1935), Acad. of Athens (Greece). Author: Alcohol, Its Effects on Man, 1934; reviser of Flint's Manual of Auscultation and Percussion, 1916. Editor: Alcohol and Man, 1932; The Baker Memorial, 1930-39, 1941, Administrative Medicine, 1942, Local Health Units for the Nation, 1945. Died May 21, 1957.

HAMILTON, Alice, Am. physician; b. N.Y.C., Feb.
27, 1869; d. Montgomery and Gertrude (Pond) H.;
M.D., U. Mich., 1893; postgrad., Germany, 1896,
Johns Hopkins, 1897, Pasteur Inst., Paris, 1902;
Sc.D., Tulane U., 1936; hon. degrees U. Mich., Holy-
oke Coll., Smith Coll., Tulane U., U. Rochester. Prof.
pathology Woman's Med. Coll., Chgo., 1897-1901;
asst. pathologist McCormick Inst., 1902-09; dir. Ill.
Commn. to Investigate Occupational Diseases, 1908-
10; with Dept. Labor, 1911-21; asst. prof. indsl.
medicine Harvard Med. Sch., later Sch. Pub. Health,
1919-35, emeritus prof., 1935—. Mem. League Na-
tions Health Com., 1924-30; cons. Internat. Labor
Office, Geneva, Switzerland, 1924—; mem. U. S. Re-
search Com. Recent Social Trends, 1923-33; pres.
Hoover's Com. on Social Trends, 1930-33. Mem.
A.M.A., A.A.A.S., Am. Pub. Health Assn. Author: In-
dustrial Poisons in the United States, 1925; In-
dustrial Toxicology, 1934; Exploring Dangerous Trades,
1943 Pioneered research in indsl. diseases. Home:
Hadlyme Ferry, Hadlyme, Conn.

KENNAWAY, Sir Ernest Laurence, English chemist, physiologist; b. May 23, 1881; s. Laurence James Kennaway; ed. Univ. Coll., London, New Coll., Oxford, Middlesex Hosp.; M.A.; M.D., Oxford U.; D.Sc., London; m. Nina Marion Derry, 1920. Dir. Chester Beatty Research Inst., Royal Cancer Hosp. (Free), London; prof. exptl. pathology U. London. Recipient Walker prize Royal Coll. Surgeons; Baly medal, 1937; Anna Fuller Meml. prize (with others), 1939; Gorton medal and prize Brit. Empire Cancer Campaign, 1946; Osler Meml. medal, 1950. Fellow Royal Soc., 1934 (Royal Medal 1941), Royal Coll. Physicians; hon. mem. several fgn. socs. Author: Some Religious Illusions in Art, Literature and Experience, 1953; also papers on cancer and biol. chemistry. Discovered prodn. of cancer by pure hydrocarbons, thus supporting theory chem. agts cause much human cancer; showed hydrocarbon in heated coal tar is responsible for many cases of indsl. cancer. Died Jan. 1, 1958.

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LEITCH, Archibald, Brit. pathologist; b. June 8, 1878; s. Neil Leitch Rothesay; ed. Glasgow (Scotland) U.; M.D.; grad. in medicine, 1902; m. Ethel MacLeod Lochhead, 1908; 1 son. Dir. Research Inst., Cancer Hosp., London; prof. exptl. pathology U. London; asst. to dir. Middlesex Cancer Research Labs., dir. Caird Research Lab., Dundee, Scotland; pathologist Cancer Hosp., London; Became research fellow St. Andrews U., Scotland, 1910. Mem. Home Office Com. Enquiry on Mule Spinners' Cancer; gen. sec. Internat. Cancer Com Mem. Leeuwenhoek Vereeniging, Path. Soc. Gt. Britain and Ireland (charter), Assn. franc pour l'etude du Cancer (corr.), German Central Commn. for Cancer Research (corr.). Editor: Report of International Cancer Conference, 1928. Died Jan. 27, 1931.

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LILIENTHAL, Howard, Am. surgeon; b. Albany, N.Y., Jan. 9, 1861; s. Meyer and Jennie (Marcus) L.; A.B. cum laude, Harvard, 1883, M.D., 1887; with McLean Asylum, br. Mass. Gen. Hosp., 1886; grad. Mt. Sinai Hosp., N.Y., 1888; m. Mary Harris d'Antignac, Oct. 19, 1891 (dec. Mar. 1910); children—Mary d'Antignac (Mrs. Thompson Lawrence), Howard; m. 2d, Edith Strode, Nov. 7, 1911. Lectr. surgery, N.Y. Polyclinic, 1888, later cons. surgeon; surgeon, Mt. Sinai Hosp., 1892-1940, Bellevue Hosp., 1909-40; prof. clin. surgery Cornell U. Med. Coll. from 1917. Fellow A.C.S. (Founders Group), Am. Bd. Surgery, A.A.A.S.; mem. Am. Soc. Control of Cancer, A.M.A., Am. Surg. Assn., Am. Soc. Thoracic Surgery (pres.), N.Y. Soc. for Thoracic Surgery (pres.), N.Y. Surg. Soc. (pres.), Med. Soc. County of N.Y. (pres.), N.Y. Acad. Medicine, Société Internat. de Chirurgie, Académie de Chirurgie (corr.). Author: Imperative Surgery, 1900; Thoracic Surgery, 1925. Contbr. to Binnie's Treatise on Regional Surgery, 1917, Ochsner's Surgical Diagnosis and Treatment, 1920; more than 300 contbns. to surg. lit. Adv. editor Jour. Thoracic Surgery. Described Lilienthal's probe for detecting bullets and metal objects in body by means of elementary electric circuit, 1910; recorded a pneumonectomy for sarcoma of lung in a tuberculous patient, 1933. Died Apr. 30, 1946.

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McCRAE, Thomas, physician; b. Guelph, Ont., Can., Dec. 16, 1870; s. David and Janet (Eckford) M.; A.B., U. Toronto, 1891, M.B., 1895, M.D., 1903; D.Sc., 1927; U. Göttingen, 1899; m. Amy Gwyn, Sept. 16, 1908. Fellow biology U. Toronto, 1892-94; asso. in medicine Johns Hopkins Hosp., 1904-12; asso. prof. medicine Johns Hopkins U., 1906-12; prof. medicine Jefferson Med. Coll., Phila., 1912—; physician to Jefferson and Pa. hosps., 1912—. Fellow Royal Coll. Physicians London (Lumleian lectr. 1924). Author: Cancer of the Stomach (with Sir William Osler), 1900. Editor: (with Osler) Modern Medicine (included McCrae's articles on typhoid fever and arthritis defor mans), 7 vols., 1907-10; Osler's System of Medicine (3d edit.); Osler's Practice of Medicine, 11th edit., 1930. Died June 30, 1935.

MEYER, Willy, surgeon; b. Minden, Westphalia, Germany, July 24, 1858; M.D., U. Bonn, 1880; m. Lily O. Maass, Apr. 29, 1885. Came to U. S., 1884. Asst. to surg. clinic U. Bonn, 1881-84; prof. clin. surgery Woman's Med. Coll., N.Y., 1886-93; instr. and prof. surgery N.Y. Post-Grad. Med. Sch. and Hosp., N.Y.C., 1887—. Introduced into U. S. cystoscopy with modification of Nitze cystoscope, 1887; 1st to perform ureteral catheterization with modified Casper instrument, 1896; 1st in U. S. to perform Bottini operation, 1897; introduced into U. S. new methods of gastrostomy; contbd. to surgery of esophagus and chest by improving cabinet for differential positive and negative pressure; suggested Meyer's solution for treatment of thromboangiitis obliterans. Died N.Y., Feb. 24 or 25, 1932.

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OSLER, William, physician; b. Bondhead, Ont., Canada, July 12, 1849; s. Featherstone Lake and Ellen Frere (Pickton) O.; ed. Trinity Coll., Toronto, 1868; M.D., McGill U., 1872; postgrad. Univ. Coll., London, univs. Berlin and Vienna, 1872-74; LL.D., McGill, 1895, Aberdeen, 1898, Toronto, 1899, Yale, 1901, Harvard, 1904, Johns Hopkins, 1905, Edinburgh, 1898; D.C.L., Trinity U., Toronto, 1902, Durham, 1913; Sc.D., Oxford, 1904, Liverpool, 1910, Dublin, 1912; m. Grace Linzee (Revere) Gross, May 1892; one son, Edward. Prof. medicine McGill U., 1874-84; prof. clin. medicine U. Pa., 1884-89; prof. principles and practice of medicine Johns Hopkins, 1889-1905; hon. prof. medicine, from 1905; physician-in-chief Johns Hopkins Hosp., 1889-1905; Regius prof. medicine Oxford U., from 1905. Student (fellow) of Christ Church Coll., Oxford. Fellow Royal Soc., 1898, also Royal Coll. Physicians. Author: The Cerebral Palsies of Children, 1889; Chorea and Choreiform Affections, 1894, Lectures on Abnormal Tumors, 1895; Angina Pectoris and Allied States, 1897; The Principles and Practice of Medicine, 1892; Cancer of the Stomach, 1900; Science and Immortality (Ingersoll lecture Harvard U.), 1904; Aequanimitas and Other Addresses, 1900; Counsels and Ideals, 1906; An Alabama Student and Other Essays, 1908; The Evolution of Modern Medicine, 1921; Incunabula Medica: a Study of the Earliest Printed Medical Books, 1467-80, 1923. Editor of System of Medicine. Renowned as physician and medical historian; numerous medical observations include those on blood platelets and abnormally high red blood cell count in polycythemia; made special study of angina pectoris; authority on spleen and heart. Died, Oxford, Eng., Dec. 29, 1919.